

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> : <b>A61K 31/00, 31/445, 31/495</b>		A1	(11) International Publication Number: <b>WO 94/18958</b> (43) International Publication Date: 1 September 1994 (01.09.94)
(21) International Application Number: <b>PCT/US93/01485</b> (22) International Filing Date: 19 February 1993 (19.02.93)		(81) Designated States: AU, CA, FI, JP, KR, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(60) Parent Application or Grant (63) Related by Continuation US Filed on 9 January 1992 (09.01.92)		Published <i>With international search report.</i>	
(71) Applicant (for all designated States except US): SAM AMER & CO., INC. [US/US]; 3177 Padaro Lane, Carpinteria, CA 93013 (US).			
(72) Inventor; and (75) Inventor/Applicant (for US only): AMER, M., Samir [US/US]; 3177 Padaro Lane, Carpinteria, CA 93013 (US).			
(74) Agents: RICHARDS, John et al.; Ladas & Parry, 26 West 61 Street, New York, NY 10023 (US).			
(54) Title: 5-HT <sub>2</sub> RECEPTOR ANTAGONIST COMPOSITIONS USEFUL IN TREATING VENOUS CONDITIONS			
(57) Abstract			
<p>Treatment of compositions containing 5-HT<sub>2</sub> receptor antagonists useful in treating such venous conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT<sub>2</sub>) at an effective therapeutic dose to treat a human or animal suffering from such a condition. The 5-HT<sub>2</sub> receptor antagonist can also be administered prophylactically.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

**5-HT<sub>2</sub> RECEPTOR ANTAGONIST COMPOSITIONS USEFUL IN**  
**TREATING VENOUS CONDITIONS**

This invention relates to the treatment of and to compositions containing 5-HT<sub>2</sub> receptor antagonists useful in treating such venous conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT<sub>2</sub>) at an effective therapeutic dose to treat a human or animal suffering from such a condition. The 5-HT<sub>2</sub> receptor antagonist can also be administered prophylactically.

Serotonin or 5-hydroxytryptamine or 5-HT is a vasoconstrictor and a powerful stimulant of a variety of smooth muscles and nerves. A derivative of the amino acid tryptophan, 5-HT is formed predominantly in enterochromaffin or argentaffin cells of the intestinal tract. It is transported in the blood by platelets and is present in the brain and other tissues. Its pharmacological actions result in a variety of responses involving, inter alia, the cardiovascular, respiratory, and gastrointestinal systems, smooth muscles, exocrine glands, carbohydrate metabolism, sensory nerve endings, autonomic ganglia, the

- 2 -

adrenal medulla, and the central nervous system.

Cellular reaction is determined by the type and number of receptors on the outer membrane of the cells. Consequently, one

5 hormone can trigger different responses in different cells because it may have different receptors. Thus, the same hormone that can contract one smooth muscle cell, can also relax a skeletal muscle cell having a different  
10 receptor to the same hormone. This is true for 5-HT.

There are many receptors for 5-HT that control the various cellular responses which are mentioned above. To identify the different

15 receptors to a specific hormone (e.g. 5-HT), several methods are used. For example, in labeling studies, the labeled hormone binds to a specific receptor. The antagonists are classified according to their ability to  
20 displace the labeled hormone from the receptor in question. Those that can displace it from a particular receptor are said to be antagonists to that receptor. Some antagonists can displace the hormone from one receptor without affecting  
25 its binding to another, and the degree of selectivity can thus be determined. In pharmacological studies, the ability of antagonists to antagonize some of the effects of the hormone thought to be related to one  
30 receptor or another are examined. A suitable example relates to the hormone histamine. Some antagonists (histamine-2 antagonists) can antagonize its acid secretory receptors with little or no effect on its lung receptors and  
35 thus inhibit acid secretion by the stomach without causing bronchodilatation. Other antagonists (histamine-1 antagonists) antagonize

- 3 -

histamine's lung effects with almost no activity against its acid secretory effects. Biochemical studies are those in which the biochemical effects of the hormone in question can be  
5 antagonized selectively by one receptor antagonist or another.

Serotonin receptors are divided into several classes, one of which is referred to as the 5-HT<sub>2</sub> receptor. A complete discussion of  
10 such receptors will be found in "The Peripheral Actions of 5-Hydroxytryptamine" edited by John R. Fozard (Oxford University Press, 1989). Receptors for 5-HT have been classified based on the responses they produce when stimulated by 5-  
15 HT. At present four main classes and several subclasses of 5-HT receptors are generally recognized. The four main classes are:

5-HT<sub>1</sub> receptors: These receptors appear to mediate the relaxation of smooth  
20 muscles and increased heart rate.

5-HT<sub>2</sub> receptors: These receptors appear to mediate vasoconstriction and platelet aggregation.

5-HT<sub>3</sub> receptors: These receptors  
25 appear to mediate vomiting by action in the central nervous system.

5-HT<sub>4</sub> receptors: These receptors mediate effects not covered by the other three receptors.

30 (P.A. van Zwieten et al. "Pathophysiological and Pharmacotherapeutic Aspects of Serotonin and Serotonergic Drugs," Clin. Physiol. Biochem. 8 (suppl 3), 1 - 18, 1990 Frazer et al. "Subtypes of Receptors for Serotonin" Ann. Rev. Pharmacol Toxicol. 30, 307 - 348, 1990)).

The Frazer article shows that serotonin has different receptors sometimes

- 4 -

mediating opposite effects. Thus a multitude of different and sometimes opposite effects can be induced by 5-HT receptor antagonists. 5-HT receptor antagonists produce different pharmacological responses depending on the type and location of the 5-HT receptor they antagonize or block. They produce a variety of different responses in the central nervous system. Peripherally, such antagonists can sometimes produce antagonistic responses. This is similar in many respects to the Histamine antagonists. Histamine-1 (H-1) antagonists inhibit bronchoconstriction but have no effect on gastric acid secretion while Histamine-2 (H-2) antagonists inhibit gastric acid secretion with no effects on the lungs. Thus a general statement that histamine antagonists should be good for acid secretion or bronchospasm is meaningless.

20           5-Hydroxytryptamine (5-HT<sub>2</sub>) receptor antagonists are different from other 5-HT receptor antagonists in many respects in that 5-HT<sub>2</sub> receptor antagonists:

- a. Antagonize serotonin stimulation of intra-cellular calcium levels via stimulation of phosphoinositide hydrolysis in smooth muscle, human and rabbit platelets and astrocytes.
- b. Antagonize serotonin contraction of the canine and human basilar artery while producing no hypotension.
- c. Antagonize the increased vascular permeability induced by 5-hydroxytryptamine
- d. Antagonize the head shakes and twitches in rodents induced by serotonin.

35           5-HT can induce both contraction and relaxation in blood vessels. The type of responses produced depends on the type of

- 5 -

receptor present. For example, 5-HT<sub>2</sub> receptor stimulation contracted the porcine coronary arteries (Daniel J. Cushing and Marlene L. Cohen, "Comparison of the Serotonin Receptors That Mediate Smooth Muscle Contraction in Canine and Porcine Coronary Artery" J. Pharmacol. Exptl. Therapy. 261, 856 - 862, 1992) but dilated the canine renal artery (Shoji et al. "Renal Vasodilation Induced by DOL, a 5-HT<sub>2</sub> Receptor Agonist, in the Canine Kidney" Europ. J. Pharmacol. 190, 247 - 250, 1990) Stimulation of 5-HT<sub>1</sub> receptors produced constriction in the canine Savenous vein (Else Muller-Schweinitzer, "Venoconstrictor Responses to Dihydroergocristine and Dihydroergotamine: Evidence for the Involvement of 5-HT<sub>1</sub> Like Receptors" Cardiovascular Drugs and Therapy, 4, 1455 - 1460, 1990), the rabbit saphenous vein, (Dicky Van Heuven - Nolsen et al. "5-HT<sub>1</sub> Like Receptors Mediate Contraction of the Rabbit Saphenous Vein" Europ. J. Pharmacol. 191, 375 - 382, 1990) but dilated the small arteriols in rat skeletal muscles (Nancy L. Alsip et al. "Multiple Serotonin Receptors on Large Arteriols in Striated Muscle" Blood Vessels, 28, 537 - 541, 1991). These are only example. For more examples see (Sahin-Erdemli et al. "5-HT<sub>1</sub> like Receptors Mediate 5-hydroxytryptamine-induced Contraction of Guinea-pig Isolated Iliac Artery" Brit. J. Pharmacol., 102, 386 - 390, 1991; Fong M. Lai et al. "Characterization of Serotonin Receptors in Isolated Rat Intramyocardial Coronary Artery" J. Pharmacol., Exptl. Therapy., 256, 164 - 168, 1991; Hubert Dabire et al., "Hemodynamic Aspects and Serotonin," Clin. Physiol. Biochem. 8 (suppl 3), 56 - 63, 1990; M.J. Summer, "Characterization of the 5-HT

- 6 -

receptor Mediating Endothelium-Dependent Relaxation in Porcine Vena Cava," Brit., J. Pharmacol., 102, 938 - 942, 1991; B.N.C.

5 Prichard and C.C.T. Smith, "Serotonin: Receptors and Antagonists - Summary of Symposium," Clin. Physiol. Biochem. 8 (suppl 3), 120 - 128, 1990, Lubo Zhang and Donald C. Dyer, "Characterization of Serotonergic Receptors Mediating Contraction of Ovine Umbilical Artery" J. Pharmacol., Exptl. Therapy. 255, 233 - 239, 1990).

In fact 5-HT can mediate both contraction and relaxation in the same tissue (Zeljko S. Radic et al., "Alterations in Serotonergic Receptor Expression in Experimental Vein Grafts;" J. Vascular Surgery 14, 40 - 47, 1991).

Tissues respond to hormones only if they possess specific receptors capable of recognizing and interacting with the hormone in question. The selective and sometimes opposite responses of different tissues to the same hormone, in this case 5-hydroxytryptamine (5-HT) or serotonin, is determined by the type and density of the receptors to the hormone that exist in the particular tissue. It is not possible to predict the activity of 5-HT receptor antagonists in a particular disease condition unless the tissue involved in that disease is tested. For example, 5-HT will not contract the colon vein of cats or dogs since the colon veins from both animals species have no 5-HT receptors. 5-HT will contract the human colon vein because the human colon vein contains 5-HT<sub>2</sub> receptors that mediate contraction. (see example below). In the human colon, 5-HT<sub>2</sub> receptor antagonists are expected to antagonize the increased contraction of the colonic veins

- 7 -

induced by 5-HT (shown in the data) and decrease the vascular permeability that mediate the swelling and discomfort of hemorrhoids. Other 5-HT receptor antagonists (as 5-HT<sub>1</sub> 1A, 1B, 1C, 5 1D, 1P and 3) will not mediate these effects and are expected to have no beneficial effects in treating hemorrhoids, varicose veins, venous insufficiency and the healing of wounds.

In the past, before the inventor's 10 present understanding of the different receptors and actions of 5-HT was discovered, it was customary to regard all 5-HT receptor antagonists as constituting one category and to assign common actions to all of them. This was 15 what was done in South African Patent 85/2785 (Merck & Co). This reference as well as U.S. Patent 4,665,075 (Vandenberk), European Patent 0037265 (Kennis), South African Patent 854161 (Merck) and U.S. Patent 4,539,318 (Baldwin) 20 suggest, without support, a connection between anti-serotonin activity and anti-hemorrhoidal effects. None of these references show any applicable data. Patents published in the 1980's generally assumed that anti-serotonin 25 activity should translate into anti-hemorrhoidal effects since the hemodynamic effects should, on theoretical grounds, be helpful. In addition, most anti-hypertensive drugs were thought to possess anti-hemorrhoidal activity. This has no 30 basis in fact.

Specific 5-HT<sub>2</sub> receptor antagonists produce several effects including inhibition of platelet aggregation and decreasing vascular permeability. 5-HT<sub>2</sub> receptor antagonist 35 compounds have traditionally been used as anti-anxiety agents, antidepressants, antipsychotics, anti-migraine agents or as modifiers of certain

- 8 -

other CNS functions. 5-HT<sub>2</sub> receptor antagonists, do not cause vasodilation in the arteries and do not lower blood pressure. This is shown in the example below where the 5-HT<sub>2</sub> receptor antagonist 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride do not lower blood pressure. This is also exemplified by ritanserine and ICI 169, 269 (Gerard J. Blauw et al., "Antihypertensive Treatment with  
10 Ketanserine Shows No Evidence of Vascular Serotonin - Receptor and alpha-Adrenoceptor Blockade" Drugs, 40 (suppl 4), 42 - 44 1990; P.A. van Zwieten et al. "The role of 5 hydroxytryptamine and 5-hydroxytryptaminergic  
15 Mechanisms in Hypertension, " Brit J. Clin. Pharmacol., 30, 695 - 745, 1990: Bengt Persson, et al., "Antihypertensive Effects of Ketanserine and Ritanserine in the Spontaneously Hypertensive Rat," J. Cardiovasc. Pharmacol., 11  
20 (suppl. 1. 522 - 524, 1988). The compounds disclosed in South African patent 85/2785 all lower blood pressure indicating that they could not be selective 5-HT<sub>2</sub> receptor antagonists.

Serotonin is not a general endogenous vasoconstrictor. Its effects in the different blood vessels varies depending on the location and size of the vessel in question (P.A. van Zwieten et al., "Pharmacological Profile of Antihypertensive" Drugs with Serotonin Receptor  
25 and alpha-Adrenoreceptor Activity Drugs 40 (suppl 4) 1 - 8, 1990). Hemorrhoids is a disease of veins not arteries. Drugs that are expected to have beneficial activity in hemorrhoids must be able to antagonize the contractile effects of 5-HT on the colon vein. Hemorrhoids is a varicose dilation of veins in  
30 the superior or inferior hemorrhoidal plexus,  
35

- 9 -

resulting from a persistent increase in venous pressure" (Dorland's Illustrated Medical Dictionary, 25th Edition, W.B. Saunders, Philadelphia, 1974).

5           Hemorrhoids refer to a madd of dilated veins in swollen tissue situated near the anal sphincter. They are believed to result from a persistent increase in venous pressure, which may be due, in part, to a constriction of the  
10          large downstream colonic veins. Occlusion due to platelet aggregation and thrombus formation may also contribute to the symptoms of hemorrhoids by interrupting blood flow and increasing blood stasis and tissue congestion.

15          Varicose veins are enlarged, twisted superficial veins. Varicose veins partially result from incompetent venous valves that may be acquired or congenital.

20          Venous insufficiency results from increase tone (partial constriction) of the deeper veins (particularly in muscles) which impedes good circulation and results in blood pooling and stasis. This is turn results in pain, tenderness and edema. The problem appears  
25          to be related to inadequate draining of the leg veins due to constriction of the exit vein valves. 5-hydroxytryptamine (5-HT or serotonin) is released from the blood platelets when the blood sits around for a long time and is thought  
30          to mediate the contraction of the exit veins.

35          In wounds, 5-HT is released from blood platelets causing venous constriction and interfering with good drainage and circulation. Good drainage and circulation are needed for proper and fast healing of the wounds.

This invention is directed to compositions or medicines useful in treating or

- 10 -

preventing such conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT<sub>2</sub>) 5 to treat an animal or human, in need of such treatment. The 5-HT<sub>2</sub> receptor antagonist can also be used prophylactically. The 5-HT<sub>2</sub> receptor antagonist is used at an effective therapeutic dose. Preferred 5-HT<sub>2</sub> receptor 10 antagonists include 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride and any mixture thereof. The 5-HT<sub>2</sub> receptor antagonist 2'-[2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride is disclosed and claimed in U.S. Patent Re. 30, 811 15 20 (Dysktra et al. Mead Johnson & Company). The 5-HT<sub>2</sub> receptor antagonist 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride is disclosed in U.S. Patents 4,338,317 and 4,487,773. The 5-HT<sub>2</sub> receptor 25 antagonist 8-[4-[4(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro [4,5] decane-7,9-dione hydrochloride is disclosed in German Patent DE 3,247,530 and U.S. Patent 4,411,901.

30 In a series of experiments using rings of human colon veins representative 5-HT<sub>2</sub> receptor antagonists were found to produce highly surprising results in blocking the contractile effects of 5-HT on the human colon.

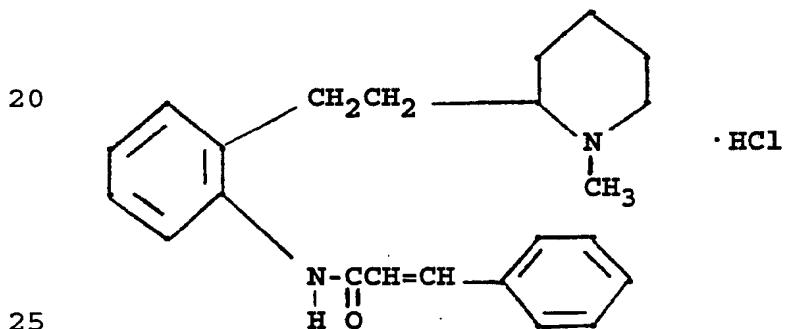
35 Human colonic vein rings were isolated from discarded human colon tissue following surgery (colostomy). The rings were prepared

- 11 -

immediately after surgery and were suspended in buffered physiological saline. The contractions produced by the rings in response to the addition of 5-HT *in vitro* were measured. The 5 effects of three selected 5-HT<sub>2</sub> receptor antagonist compounds on antagonizing 5-HT contractile effects were also determined.

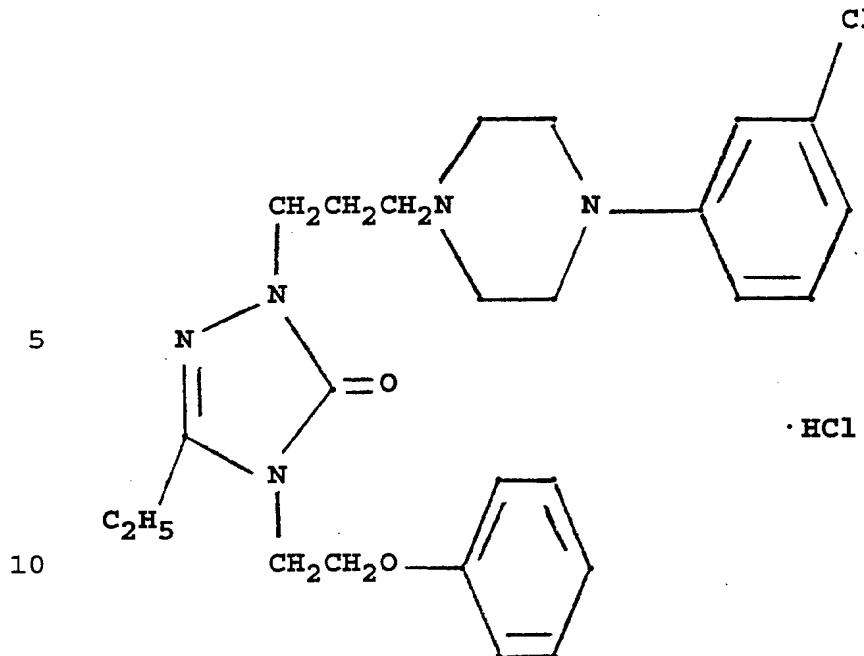
The following tables list the three compounds used and the activity of each in blocking the contractile effects of 5-HT on the 10 human colon *in vitro*. Table A also includes the activities of the three compounds on four receptors to determine receptor selectivity.

Compound I as used herein has the 15 chemical formula: 2' [2-(1-methyl-2-piperidyl)ethyl] cinnamanilide hydrochloride, and has the following structural formula:

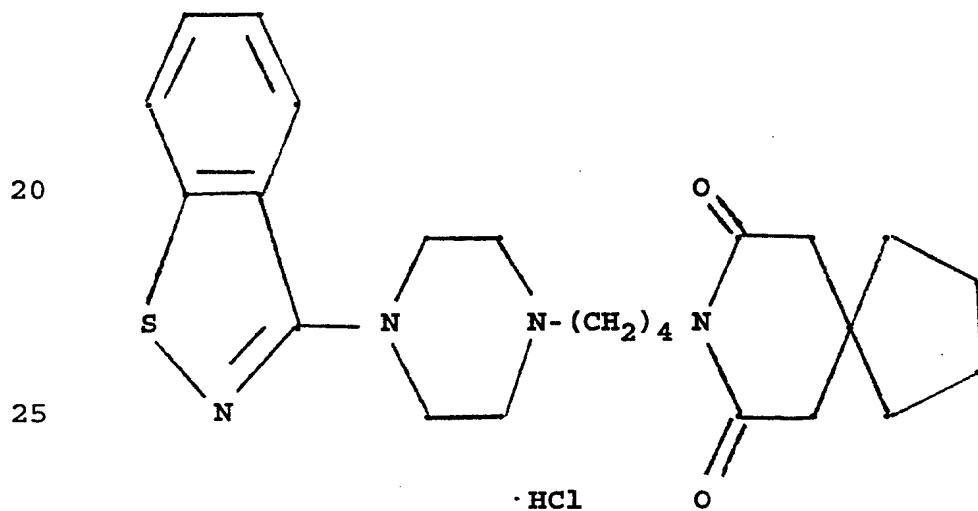


Compound II as used herein has the chemical 20 formula: 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, and has the following structural 25 formula:

- 12 -



Compound III as used herein has the chemical formula: 8-[4-[4-(1,2-benzisotiazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride, and has the following structural formula:



- 13 -

Table A

Receptor Blocking Profile (IC - 50; nm) [nM == nanomolar or 1x 10<sup>-9</sup>M]

Receptor	Compound I	Compound II	Compound III
5	5-HT <sub>2</sub>	3.4	17.0
	5-HT <sub>1</sub>	22,000.0	>1,000.0
	Dopamine-2	>1000.0	>1000.0
	Alpha-receptor	>1000.0	160.0
			47.0

The IC-50 is the concentration that  
 10 inhibits agonist binding to the receptor by 50%.  
 The better the blocker a compound is, the  
 smaller is the concentration thereof needed to  
 block the receptor, i.e., the smaller the IC-50,  
 the better receptor blocker or antagonist the  
 15 compound is.

The activity is determined as follows:  
 Rings of human colon veins are prepared and hung  
 in a tissue bath. The contractions of the rings  
 are monitored. Adding 5-HT causes the rings to  
 20 contract. Pre-addition of increasing  
 concentrations of the antagonist result in  
 lesser contractions. The amount of antagonist  
 causing a 50% inhibition of the contractions is  
 then calculated.

The receptor blocking profile is  
 determined as follows: Labeled 5-HT is mixed  
 with a purified preparation containing the  
 receptor. The amount of labeled material that  
 attaches itself to the receptor and cannot be  
 30 washed off is calculated. In a series of other  
 similar tubes, the same quantity of labeled 5-HT  
 is mixed with increasing concentrations of the  
 antagonist which will antagonize the binding of  
 5-HT to the receptor. Decreasing quantities of  
 35 the labeled material will bind to the receptor.  
 The concentration of the antagonist that  
 inhibits the binding of 50% is then calculated.

- 14 -

Table B

Activity against 5-HT on the human colon in vitro

IC-50     $2 \times 10^{-9}$  (I)    $10^{-8}$  (II)    $10^{-9}$  (III)

5           As is evident from the above data, although the compounds I, II, and III possess widely different activities against the different receptors tested, their activities in blocking the contractile effects of 5-HT on  
10          human colon rings correlated best with their 5-HT<sub>2</sub> blocking potencies.

15          Since these three compounds differ significantly from each other chemically, one can conclude that their antagonism of the effects of 5-HT on the human colon is due primarily to their function in blocking the 5-HT<sub>2</sub> receptors in that tissue. Thus, other 5-HT<sub>2</sub> receptor antagonists, irrespective of their chemical structure or other properties, should  
20          antagonize 5-HT and block its contractile effects on the human colon.

25          An experiment was performed and established that 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride (MPEC) does not lower blood pressure. This is a classical pharmacological experiment designed to test the effects of new drugs on blood pressure:

30          Beagle hounds of either sex weighing 8 - 20 kg were acclimated (18 - 29°C, humidity 30 - 70%) for a minimum of 21 days with automatically controlled illumination (12 hours light/12 hours dark) prior to use.  
35          Each animal received approximately 300 grams of Purina Lab Canine Diet #5006 daily which was adjusted as needed for each animal to maintain appropriate body weight. Husbandry practices and veterinary care

- 15 -

were in accordance with the Guide for Care  
and Use of Laboratory Animals (NIH  
Publication No. 85 - 23)

5       Animals were fasted on the morning of the  
experiment and anesthetized with  
pentobarbital sodium 35 mg/kg i.v. Each  
animal was intubated with cuffed  
endotracheal tube to maintain respiration  
with Bird Mark 7 respirator. Arterial  
10      blood pressure (right femoral artery) was  
measured with Statham P23Db or P23Gb  
pressure transducer (Gould Statham  
Instruments, Halo Rey, PR). Heart rate was  
calculated from the pressure recordings.  
15      Other parameters were also monitored. The  
right femoral vein was cannulated for  
administration of supplemental anesthesia,  
and the left femoral vein for  
administration of vehicle or test drug.  
20      When give intravenously, MPEC in a dose of  
1 mg/kg elicited no effect on blood  
pressure or heart rate. A dose of 10 mg/kg  
was lethal in both dogs tested.

25      The effects of MPEC on patients with  
hemorrhoids was studied. This was a double-  
blind study. The drug was applied as a 1% cream  
three times a day. Patients maintained a  
symptom diary each day. The diary included  
evaluation of each symptom on a 10 point scale.  
30      The results described represent the improvements  
in the scale between days 1 and 5. The results  
are depicted in the accompanying graph. The  
actual numbers of score improvements were as  
follows:

- 16 -

<u>Parameter</u>	<u>Placebo</u>	<u>MPEC</u>	<u>% Improvement</u>
Pain	0.71	2.14	301.4
Itching	1.42	2.00	140.8
Bleeding	-0.43	1.43	>1000.0
5 Tenderness	0.86	2.71	315.1
Fullness	0.80	4.50	562.5
Throbbing	0.80	1.75	218.8

The results also support the conclusion that MPEC is working in hemorrhoids via 5-HT<sub>2</sub> receptor blockade since the main effect appears to be on fullness and bleeding. It is expected that a product blocking 5-HT<sub>2</sub> receptors in the colon veins will help with the drainage and will reduce the feeling of fullness that patients with hemorrhoids feel. Since there will be less blood trapped in the swollen veins, less bleeding is also expected. None of the medications presently available on the market have an effect on these two parameters.

The 5-HT<sub>2</sub> receptor antagonists of this invention may be used topically or systemically, and they may be taken orally, in liquid, powder, table or capsule form; parenterally, by intravenous, subcutaneous, or intramuscular injection; transdermally, topically by direct application in the form of a cream, gel, or ointment; rectally by suppository or enema; or by inhalation therapy. The 5-HT<sub>2</sub> receptor antagonists of this invention may be prepared and used in any suitable solid or liquid form, e.g. powder, cream, paste, table, lozenge, gel, chewing gum, solution, suspension, emulsion, salve, aerosol or the like. They may also be incorporated into wound dressings such as bandages, adhesive strips, and other forms designed to be used for wounds. These pharmacological agents may be administered in

- 17 -

admixture with a pharmaceutically acceptable carrier or a dermatologically acceptable carrier for the topical preparations.

The compositions contain the active 5 ingredient in an amount ranging from less than 1% to over 99%, with the remainder being a pharmaceutically acceptable or dermatologically acceptable solid or liquid carrier, which may contain other conventional excipients. Example 10 of such carriers and excipients include fillers, binders, flavors, sweetners, bulking and coloring agents, antioxidants, anionic, nonionic, cationic, zwitterionic, and amphoteric 15 surface active detergents, sudsing, dispersing and emulsifying agents, buffering and pH adjusting agents, water and organic solvents, humectants, thickeners, preservatives, stabilizers, mold release agents, disintegrates, anti-distingegrants, lubricants and the like. 20 Examples of conventional pharmaceutically acceptable carriers and excipients are profusely disclosed in the prior art including discussions in U.S. 4,515,772 (Parran et al. Procter & Gamble), U.S. 4,966,777 (Gaffar et al., — 25 Colgate-Palmolive Company), and U.S. 4,728,512 (Mehta et al. American Home Products), which discussions are incorporated herein by reference thereto.

The topical compositions typically 30 contain from 0.1 to 20 weight % of a 5-HT<sub>2</sub> receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1 - 5 weight %.

Transdermal compositions typical 35 contain from 0.1 to 20 weight % of a 5-HT<sub>2</sub> receptor antagonists. Preferably, they contain from 0.5 to 10 weight %. More preferably, from

- 18 -

1- 5 weight %.

Suppositories typically contain from 0.1 to 20 weight % of a 5-HT<sub>2</sub> receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1- 5 weight %.

Wound dressings typically contain from 0.1 to 20 weight % of a 5-HT<sub>2</sub> receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1- 5 weight %.

Suitably the compositions of this invention consist of sufficient material to provide a dose of from 0.05 - 10 mg. per kg. of body weight, more suitably 0.2 - 6 mg/kg body weight. These compositions may be taken 1 - 3 times daily or as needed until the pain or symptoms of the conditions have subsided.

It will be understood that the foregoing discussion including the examples, only illustrates the invention and its principles. However, many modifications and variations in the details of the disclosure will occur to those skilled in the art to which this invention relates and still remain within the scope and principles of the invention. For example, the illustrative embodiments of the invention deal primarily with several specific 5-HT<sub>2</sub> receptor antagonists. It is apparent, however, that the principles of the invention can be applied to other 5-HT<sub>2</sub> receptor antagonists as well.

- 19 -

C L A I M S

1. Use of a 5-HT<sub>2</sub> receptor antagonist for the manufacture of a medicament for the treatment or prevention of venous conditions.
- 5 2. A medicine for treatment or prevention of venous conditions characterized in that the medicine comprises a therapeutically acceptable amount of a 5-HT<sub>2</sub> receptor antagonist in a carrier.
- 10 3. A method of treating or preventing venous conditions such as hemorrhoids, varicose veins, venous insufficiency or wound healing characterized by administering to an afflicted or susceptible patient a 5-HT<sub>2</sub> receptor antagonist at a therapeutically effective dose.
- 15 4. Use of a 2-HT<sub>2</sub> receptor antagonist to treat or prevent hemorrhoids, varicose veins, venous insufficiency or wounds.
- 20 5. A medicine, use or treatment according to any one of the preceding claims, wherein the 5-HT<sub>2</sub> receptor antagonist is 2' [2-1-methyl-2-piperidyl] ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H=1,2,4-triazol-3-one hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride or any mixture thereof.
- 25 6. A medicine, use or treatment according to any one of the preceding claims, wherein the venous conditions are hemorrhoids, varicose veins, venous insufficiency or wound healing.
- 30 7. A topical composition characterized by a 5-HT<sub>2</sub> receptor antagonist in a dermatologically acceptable carrier.
- 35 8. A topical composition according to Claim 7, wherein the 5-HT<sub>2</sub> receptor antagonist

- 20 -

is 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride or any mixture thereof.

9. A topical composition according to Claims 7 or 8, wherein the amount of the 5-HT<sub>2</sub> receptor antagonist is from 0.1 to 20 wt %.

10. A topical composition according to Claims 7-9, wherein the amount of the 5-HT<sub>2</sub> receptor antagonist is from 0.5 to 10 wt %.

11. A suppository characterized by a 5-HT<sub>2</sub> receptor antagonist in a pharmaceutically acceptable carrier.

12. A suppository according to Claim 11, wherein the 5-HT<sub>2</sub> receptor antagonist is 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride or any mixture thereof.

13. A suppository according to Claims 11-12, wherein the amount of the 5-HT<sub>2</sub> receptor antagonist is from 0.1 to 20 wt %.

14. A suppository according to Claims 11-13, wherein the amount of the 5-HT<sub>2</sub> receptor antagonist is from 0.5 to 10 wt %.

15. A wound dressing characterized by a 5-HT<sub>2</sub> receptor antagonist in an acceptable carrier.

16. A wound dressing according to claim 15, wherein the 5-HT<sub>2</sub> receptor antagonist is

- 21 -

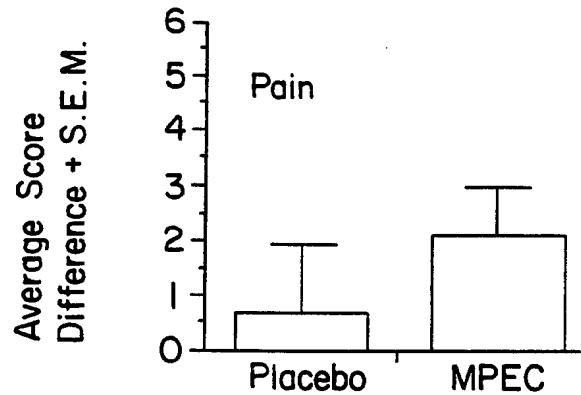
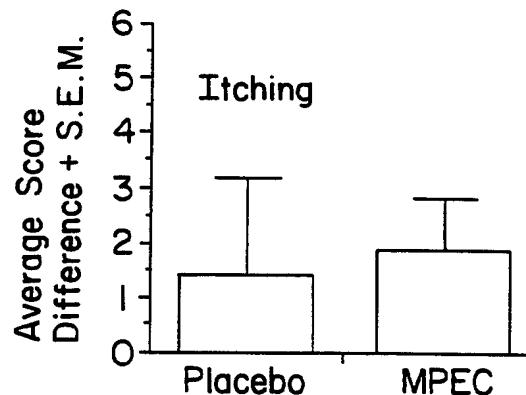
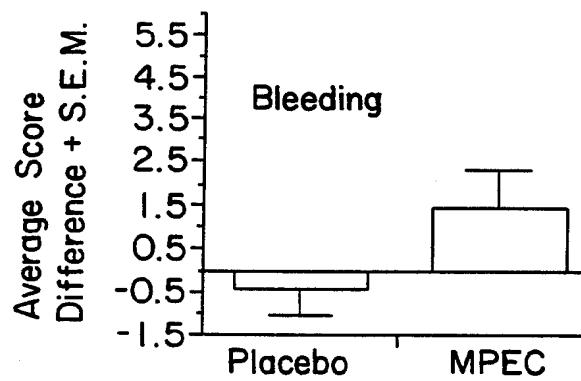
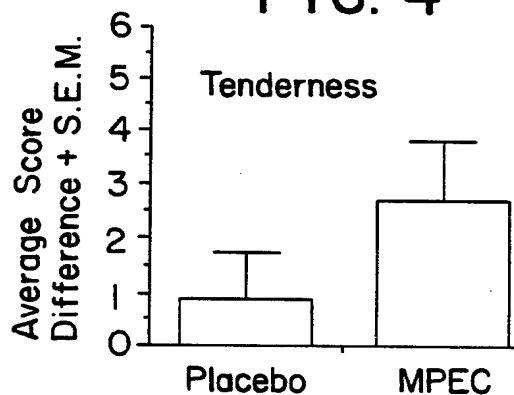
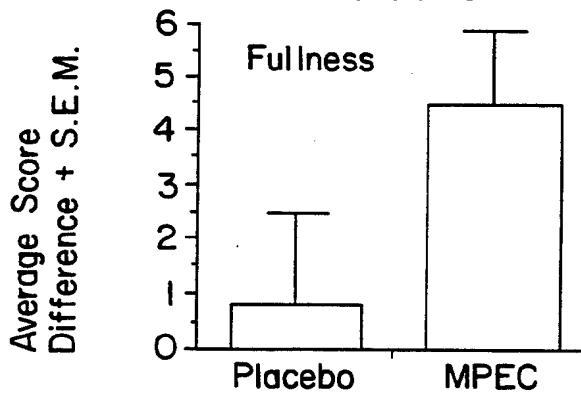
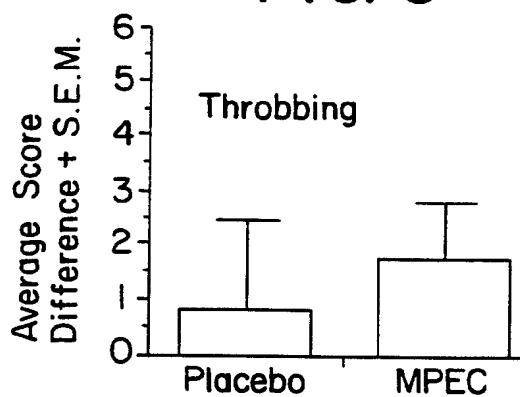
2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one

5 hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride or any mixture thereof.

17. A wound dressing according to claims 15 or 16, wherein the amount of the 5-HT<sub>2</sub>

10 receptor antagonist is 0.1 to 20 wt.%.

18. A wound dressing according to claims 15-17, whrein the amount of the 5-HT<sub>2</sub> receptor antagonist is from 0.5 to 10 wt.%.

**FIG. 1****FIG. 2****FIG. 3****FIG. 4****FIG. 5****FIG. 6**

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 93/01485

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K31/00; A61K31/445; A61K31/495		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	US,A,4 064 254 (DYKSTRA ET AL.) 20 December 1977 * see column 2 lignes 35 - 55 ; claims 11-20 *	2,5,6
X	US,A,4 411 901 (TEMPLE JR) 25 October 1983 * column 12 lines 22-55; claims 1-9, 12 *	2,5-8
X	US,A,4 487 773 (TEMPLE JR.) 11 December 1984 * see colonne 8 lignes 41-68; the claims * * column 4 lines 30 -31 *	2,5-8
Y	---	1,3,4, 9-10, 15-18
	---	-/-
* Special categories of cited documents : <sup>10</sup> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search  27 SEPTEMBER 1993	Date of Mailing of this International Search Report  12.10.93	
International Searching Authority  EUROPEAN PATENT OFFICE	Signature of Authorized Officer  B. ISERT	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	DERMATOLOGICA vol. 178, 1989, pages 98 - 102 ROELENS P., 'Double-blind placebo-controlled study with topical 2% ketanserin ointment in the treatment of venous ulcers' * see the whole document * * p. 98 "Introduction" ---	1-4, 6, 7, 9-10, 15, 17, 18
Y		1, 3, 4, 9, 10, 15-18
X	EP,A,0 526 434 (BOEHRINGER INGELHEIM ITALIA) 3 February 1993 * see page 10 lines 12-16, and page 13 lines 35-42 ---	2, 6, 7, 11
X	PROG. CLIN. BIOL. RES. vol. 365, 1991, pages 115 - 128 ROOMAN RP. ET AL. 'Ketanserin promotes wound healing: clinical and preclinical results' * see the whole document * * see pages 115-118, 124 -125 (discussion) -----	1-4, 6, 7, 9, 10, 15, 17, 18
Y		1, 3, 4, 9, 10, 15-18

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9301485  
SA 71521

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/09/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4064254	20-12-77	US-A- 3931195 US-A- 4000143 US-E- RE30812 US-E- RE30811 AU-A- 3914572 BE-A- 779951 CA-A- 961038 CH-A- 587821 CH-A- 578529 CH-A- 596177 DE-A,C 2210154 FR-A,B 2128584 GB-A- 1346261 NL-A- 7811882 NL-A- 7202614	06-01-76 28-12-76 01-12-81 01-12-81 23-08-73 28-08-72 14-01-75 13-05-77 13-08-76 28-02-78 21-09-72 20-10-72 06-02-74 27-04-79 05-09-72
US-A-4411901	25-10-83	AT-B- 383124 AU-B- 550780 AU-A- 9087282 BE-A- 895469 CA-A- 1205806 CA-C- 1216586 CH-A- 659070 CH-A- 656617 DE-A- 3247530 DE-A- 3250090 FR-A,B 2521561 FR-A,B 2531431 GB-A,B 2114119 JP-A- 5017457 LU-A- 84550 NL-A- 8204910 SE-B- 453502 SE-A- 8207350 SE-B- 462162 SE-A- 8702389 US-A- 4452799	25-05-87 10-04-86 23-06-83 23-06-83 10-06-86 13-01-87 31-12-86 15-07-86 30-06-83 12-12-91 19-08-83 10-02-84 17-08-83 26-01-93 08-09-83 18-07-83 08-02-88 10-08-83 14-05-90 09-06-87 05-06-84
US-A-4487773	11-12-84	US-A- 4338317 AT-B- 388555	06-07-82 25-07-89

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9301485  
SA 71521

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/09/93

Page 2

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4487773		AU-B- 579826	15-12-88
		AU-A- 2995384	03-01-85
		BE-A- 900038	28-12-84
		CA-A- 1255310	06-06-89
		CH-A- 663412	15-12-87
		CH-A- 662562	15-10-87
		DE-A- 3423898	03-01-85
		FR-A- 2551439	08-03-85
		GB-A, B 2142631	23-01-85
		GB-A- 2184446	24-06-87
		GB-A, B 2184447	24-06-87
		GB-A, B 2185021	08-07-87
		JP-B- 5024151	06-04-93
		JP-A- 60036469	25-02-85
		LU-A- 85442	26-03-85
		NL-A- 8402028	16-01-85
		SE-A- 8403460	30-12-84
		US-A- 4575555	11-03-86
		AT-B- 384022	25-09-87
		AU-A- 8117082	23-09-82
		BE-A- 892503	15-09-82
		CA-A- 1198436	24-12-85
		CH-A- 649539	31-05-85
		DE-A, C 3209557	09-12-82
		FR-A, B 2501690	17-09-82
		GB-A, B 2096137	13-10-82
		JP-C- 1611799	30-07-91
		JP-B- 2037353	23-08-90
		JP-A- 57159774	01-10-82
		LU-A- 84011	22-02-83
		NL-A- 8201021	18-10-82
		SE-B- 447256	03-11-86
		SE-A- 8201631	17-09-82
EP-A-0526434	03-02-93	AU-A- 2427592	02-03-93
		WO-A- 9303016	18-02-93